REMARKS

Applicant notes with appreciation the Examiner's acknowledgement and acceptance of the Request for Continued Examination as well as the overcoming of the new matter rejection of claims 33 and 34 and the rejection of claims 28-31 under 35 USC 102(b) in view of Cannes.

As requested, Applicant submits herewith a new Information Disclosure Statement and PTO Form 1449 setting forth and enclosing those references not previously indicated as having been considered by the Examiner.

Applicant appreciates the Examiner pointing out the requirement for cancellation of non-elected claims to be fully responsive to a final rejection. However, with the filing of the Request for Continued Examination, the application is no longer under final rejection, and thus the requirement to cancel the non-elected subject matter is premature.

Status of Claims

By the foregoing amendments, claims 28, 29, 31, 32, and 36-66 are pending in the application. Claims 30, 33, 34, and 35 have been cancelled without prejudice. Claims 28, 29, 31, 32, and 36 were previously examined and considered by the Examiner, and have been further amended to more clearly point out the present invention. New claims 37-66 have been presented. No new matter has been introduced.

In a sincere effort to expedite prosecution of this application, all of the pending claims, both previously existing and newly added, have been limited to the method of making cross-over chemokine proteins.

Claims 28 and 29 have been amended to incorporate the subject matter of previously dependent, and now cancelled, claim 30 so as to limit the claims to chemokine proteins. Claim 32 has been amended in a likewise manner to incorporate the subject matter of the previously dependent, and now cancelled, claim 33 so as to limit the claims to chemokine proteins. This amendment necessitated the cancellation of claims 34 and 35.

New independent claims 56 and 66 have been added, with claim 56 directed to the method of making a cross-over chemokine protein with a single ligation site and claim 66 directed to the method of making a cross-over chemokine protein from two peptide segments with different amino acid sequences where the first peptide segment has an N-terminal cysteine and the second peptide segment has a C-terminal thioester. Support for these claims can be found throughout the specification, and particularly at pages 28-29.

New claim 37 is similar to claim 36, but depends from claim 29 instead of claim 28.

New claims 38-41 (depending from independent claim 28), claims 47-50 (depending from independent claim 32), and claims 57-60 (depending from claim 56) are directed to chemical tags. Support for these claims can be found at pages 8, 15 and 18.

New claims 42, 51, and 61 are directed to the use of chemokine protein segments derived from different subfamilies. Support for these claims can be found at pages 26 and 39.

New claims 43, 52, and 62 are directed to the use of chemokine protein segments derived from different species. Support for these claims can be found at page 13.

New claims 44, 53, and 63 are directed to the method of preparation of the chemokine proteins. Support for these claims can be found at pages 13-14.

New claims 45, 46, 54, 55, 64 and 65 are directed to the chemical modification of the chemokine proteins. Support for these claims can be found at pages 8, 9, 13, 15, and 18.

Rejection of Claims 28-36 Under 35 USC 112 (New Matter Rejection)

Claims 28-36 have been rejected under 35 USC 112, first paragraph, as containing new matter with regard to the terminology "sufficient homology to a functional domain of a chemokine, macrophage migration inhibitory factor, cytokine, trefoil peptide, growth factor, protease inhibitor, or protein toxin" since support for such language in the specification was not noted by the Examiner. This rejection is believed to be obviated by the foregoing amendments to independent claims 28 and 32 where this language was deleted.

The language in claims 28-36 has been changed to read "sufficient homology to a functional protein module of a chemokine". Support for this language can be found

throughout the specification. See for example, the first full paragraph on page 8, and the definition of a functional protein module on page 7.

This amendment to the claim is believed to fully address the Examiner's concerns. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Rejection Under 35 USC 112 - Claims 28-36 (Written Description)

Claims 28-36 have been rejected under 35 USC 112, first paragraph, as containing an inadequate written description since, in the Examiner's view, the specification does not provide support for a genus of cross-over proteins devoid of sequence length, amino acid content, specific biological function wherein each of the protein segments exhibit "sufficient homology to a functional domain of a chemokine, macrophage migration inhibitory factor, cytokine, trefoil peptide, growth factor, protease inhibitor, or protein toxin." This rejection is respectfully traversed and is believed to be obviated by the foregoing amendments which have deleted the objected to language and the following remarks.

The Revised Interim Written Description Guidelines Training Materials posted on the U.S. Patent Office's website make it clear at page 4 that

> "There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. If the examiner determines that the application does not comply with the written description require, the examiner has the initial burden, after a through reading and evaluation of the content of the application, of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support of the claims.

The presently amended claims are directed to a method of forming a cross-over chemokine protein that contains at least one peptide segment whose sequence is derived from a first chemokine protein, and at least one peptide segment whose sequence is derived from a second chemokine protein, wherein said second chemokine protein has an amino acid

sequence that is different from that of said first chemokine protein. These claims are clearly supported by the present specification, which provides a clear written description of the present invention sufficient to convey to others that the applicants had possession of the claimed invention at the time of filing of the application.

The specification discloses examples that are representative of the claimed genus, which by the foregoing amendments is clearly limited to peptide segments with a chemokine protein module that is derived from a chemokine protein. This disclosure in the specification clearly shows to one skilled in the art that the Applicants had possession of the claimed invention and that this was conveyed through the written description in the specification.

Applicant further notes that the presently claimed invention more closely tracks the situation of Amgen Inc. v. Hoechst Marion Roussel Inc., 314 F.3d 1313 (Fed. Cir. 2003), which distinguished the University of California v. Eli Lilly & Co., 119 F.2d 1559, 43 USP2d 1398 (Fed. Cir.) and marked a further departure by the Federal Circuit from rigorous application of the Lilly rule. The claims at issue in Amgen were directed to expression of exogenous erythropoietin (EPO)-a hormonal substance that stimulates red blood cell formation-in vertebrate and mammalian cells, but the specification disclosed methods of producing EPO only in hamster and monkey cells. The defendants in Amgen relied upon Lilly and Enzo II to support their position that Amgen's patents lacked adequate written description for the generic claims covering vertebrate and mammalian EPO-producing cells. However, the court emphatically found both Lilly and Enzo II inapposite to the case at bar "because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend" but instead "refer to types of cells that can be used to produce recombinant human EPO." Id. at 1332.

The court thus distinguished Lilly, noting that, in contrast to the relative lack of description of an actual DNA sequence by the term "cDNA," the words "mammalian cells" and "vertebrate cells" "readily 'convey distinguishing information concerning [their] identity' such that one of ordinary skill in the art could 'visualize or recognize the identity of those members of the genus.' " Id. (quoting Lilly, 119 F.3d at 1567, 1568). Accordingly, the court

affirmed the finding that the specification's description of producing the claimed EPO in two species of vertebrate and mammalian cells adequately supported claims covering EPO made using the entire genus of vertebrate or mammalian cells. Id.

In the presently claimed invention, the terms used in the claims "readily 'convey distinguishing information concerning [their] identity' such that one of ordinary skill in the art could 'visualize or recognize the identity of those members of the genus.' " as required by Lilly. Hence, the presently claimed invention clearly complies with the written description requirement.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Rejection of Claims 28-31 Under 35 USC 103(a)

Claims 28-31 have been rejected under 35 USC 103(a) as being unpatentable over Canne et al., JACS Vol. 117 (1995) pages 2998-3007; Dawson et al. Science Vol. 266 (11/94) pages 776-779 and Clarke-Lewis et al., J. Biol. Chem. Vol. 269, No. 23 (June 10, 1994) pages 16075-16081. This rejection is respectfully traversed in view of the foregoing amendments and the following remarks. Accordingly, reconsideration of the same is respectfully requested.

Applicant believes that Canne et al., Dawson et al., and Clarke-Lewis et al., either alone or in combination, do not teach or even suggest the presently claimed invention for the reasons set forth in Applicants' prior responses, which are hereby incorporated by reference.

In fact, as noted by the Examiner, Canne et al., either alone or in combination with Dawson et al., simply fails to "disclose the selection of peptide segments from chemokine proteins for producing a cross-over [chemokine] protein."

Clarke-Lewis was then cited to show "the use of peptide fragments derived from chemokines (e.g. IL-8) comprising two or more functional domains (e.g. CXC and CC chemokine families; see page 16075) for making hybrid proteins comprising peptide fragments comprising IL-8 domain regions." From this, it was concluded that it would have

been obvious to one skilled in the art to have used the method of Canne et al. an/or Dawson et al. to make the Clarke-Lewis chemokine hybrids.

Applicant respectfully disagrees with this conclusion for a number of reasons that are elucidated below.

Firstly, Applicant notes that a claimed invention is unpatentable if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a) (Supp. 1998); see Graham v. John Deere Co., 383 U.S. 1, 14, 148 USPQ 459, 465 (1966). The ultimate determination of whether an invention is or is not obvious is a legal conclusion based on underlying factual inquiries including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence of nonobviousness. See Graham, 383 U.S. at 17-18, 148 USPQ at 467; Miles Labs, Inc., Inc. v. Shandon Inc., 997 F.2d 870, 877, 27 USPQ2d 1123, 1128 (Fed. Cir. 1993).

A rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references is necessary to avoid the subtle but powerful attraction of a hindsight-based obviousness analysis . See, e.g., C.R. Bard, Inc. v. M3 Sys., Inc., 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed. Cir. 1998) (describing "teaching or suggestion or motivation [to combine]" as an "essential evidentiary component of an obviousness holding"); In re Rouffet, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998) ("the Board must identify specifically . . . the reasons one of ordinary skill in the art would have been motivated to select the references and combine them"); In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (examiner can satisfy burden of obviousness in light of combination "only by showing some objective teaching [leading to the combination]"); In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) (evidence of teaching or suggestion "essential" to avoid hindsight); Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 297, 227 USPQ 657, 667 (Fed. Cir. 1985) (district court's conclusion of obviousness was error when it "did not elucidate any factual teachings,

suggestions or incentives from this prior art that showed the propriety of combination"). See also Graham, 383 U.S. at 18, 148 USPQ at 467 ("strict observance" of factual predicates to obviousness conclusion required). Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. See, e.g., Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985) ("The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time."). In this case, it appears that the Examiner has fallen into the hindsight trap.

As noted in In re Dembiczak, 175 F.3d 994, 998, 50 USPQ2d 1614, 1616 (Fed. Cir. 1999), there must be a suggestion, teaching, or motivation to combine the teachings of the references. This may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved, see Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1630 (Fed. Cir. 1996), Para-Ordinance Mfg. v. SGS Imports Intern., Inc., 73 F.3d 1085, 1088, 37 USPQ2d 1237, 1240 (Fed. Cir. 1995), although "the suggestion more often comes from the teachings of the pertinent references," Rouffet, 149 F.3d at 1355, 47 USPQ2d at 1456. The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular. See, e.g., C.R. Bard, 157 F.3d at 1352, 48 USPQ2d at 1232. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not "evidence." E.g., McElmurry v. Arkansas Power & Light Co., 995 F.2d 1576, 1578, 27 USPQ2d 1129, 1131 (Fed. Cir. 1993) ("Mere denials and conclusory statements, however, are not sufficient to establish a genuine issue of material fact."); In re Sichert, 566 F.2d 1154, 1164, 196 USPQ 209, 217 (CCPA 1977) ("The examiner's conclusory statement that the specification does not teach the best mode of using the invention is unaccompanied by evidence or reasoning and is entirely inadequate to support the rejection."). In addition to demonstrating the propriety of an obviousness analysis, particular factual findings regarding the suggestion, teaching, or motivation to combine serve a number of

important purposes, including: (1) clear explication of the position adopted by the Examiner and the Board; (2) identification of the factual disputes, if any, between the applicant and the Board; and (3) facilitation of review on appeal.

Here, there is no suggestion, teaching, or motivation to combine the various teachings of the cited Canne et al., Dawson et al. and Clarke-Lewis et al. references other than through a hindsight analysis. One skilled in the art at the time the presently claimed invention was made, would not have been motivated to combine these references in the manner urged by the Examiner. For example, although Canne et al. and Dawson et al. disclose chemical ligation of certain types of proteins, they are silent as to the use of chemical ligation to make chemokines, much less cross-over chemokines. Likewise, although Clarke-Lewis et al. teach the use of step-wise chain assembly for making "hybrid" chemokines (p. 16076 "Experimental Procedures"), they are completely silent on using chemical ligation for this purpose.

Furthermore, one skilled in the art would not have been motivated to attempt to combine the references as urged by the Examiner in view of the lack of any suggestion, reason or motivation to do so, particularly in view of a lack of any expected benefit or expectation of success of using chemical ligation to try and make hybrid chemokines, much less cross-over chemokines. In fact, the express teachings of Clarke-Lewis et al. would have motivated one of ordinary skill to make chemokines using step-wise chain assembly, and not by the presently claimed method of chemical ligation.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Rejection of Claims 32-36 Under 35 USC 103(a)

Claims 32-36 have been rejected under 35 USC 103(a) as being unpatentable over Canne et al., JACS Vol. 117 (1995) pages 2998-3007; Dawson et al. Science Vol. 266 (11/94) pages 776-779 and Clarke-Lewis et al., J. Biol. Chem. Vol. 269, No. 23 (June 10, 1994) pages 16075-16081 and further in view of Pavia et al., Biorg. & Medicinal Chem. Lett. Vol. 3, No. 3 pages 387-396. This rejection is respectfully traversed in view of the foregoing amendments

and the above remarks and the following comments. Accordingly, reconsideration of the same is respectfully requested.

For the reasons noted above, none of Canne et al., Dawson et al, and Clarke-Lewis et al., either alone or in combination, disclose or even suggest the presently claimed invention. Furthermore, there simply is no suggestion to combine the references as urged by the Examiner.

The addition of the disclosure and teachings of Pavia et al. does not remedy this deficiency. As noted in Applicants' prior responses, the multiple synthetic approaches discussed in Pavia et al. is merely a general review of combinatorial chemistry methods unrelated to the presently claimed joining, by any means or in any orientation, of peptide domains of different chemokine proteins to form a library of cross-over chemokine proteins.

Additionally, there is no suggestion or motivation for attempting to combine the teachings of Pavia et al. with that of Canne et al., Dawson et al., and Clarke-Lewis et al., and even if such combination were to be attempted on the basis of improper hindsight analysis, it still would not disclose or suggest the presently claimed invention.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Obvious Type Double Patenting Rejections

Claims 28-36 have been rejected under the judicially created doctrine of obviousness type double patenting in light of U.S. Patent Nos. 6,184,344 and 6,326,468 in view of Canne et al., alone or in further combination with Pavia et al.

As noted in Applicants' prior response, in the interest of advancing the prosecution of the present application, and not as an acquiescence to the merits of the Examiner's arguments, Applicants respectfully advise that should the Examiner conclude that the amended claims define patentable and allowable subject matter that would have been obvious in light of the claims of the 6,184,344 and the 6,326,468 patents, Applicants will terminally disclaim such portion of any patent that will issue on such claims that will extend beyond the terms of U.S.

Patent Nos. 6,184,344 and the 6,326,468. Applicants agree to promptly provide a terminal disclaimer upon notification of such allowable subject matter.

CONCLUSION

Having now fully responded to the issues raised by the Examiner, Applicants respectfully submit that the present application is now in condition for allowance and earnestly solicit early notice of such favorable action.

Should the Examiner have any questions with respect to any issues regarding this application, he is respectfully urged to contact the undersigned.

It is not believed that extensions of time or fees are required, beyond those, which may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 50-0548 and prompt notification of the undersigned is requested.

Respectfully submitted,

Date: October 21, 2003

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